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Review

European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN

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Abstract: Influenza may cause severe disease and mortality in leukemia patients and in hematopoietic stem cell transplantation recipients. The 4th European Conference of Infections in Leukemia (ECIL-4) has developed evidence-based guidelines for prevention and management of influenza infections in these patients. Real-time reverse-transcription polymerase chain reaction is the diagnostic test of choice, as it is the most sensitive and specific test for influenza. The risks for severe influenza and fatal outcome include lymphopenia, older age, influenza soon after transplantation or chemotherapy, steroid treatment, and lack of early antiviral therapy. Neuraminidase inhibitors (oral oseltamivir or inhalation of zanamivir) are currently the most effective therapeutic agents for influenza. Main preventive measures include annual vaccination of patients, household contacts, and hospital staff. This review summarizes ECIL-4's main recommendations.

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Key words: influenza; hematopoietic stem cell transplantation; HSCT; leukemia; The European Conference on Infections in Leukemia; ECIL-4; guidelines; recommendations

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Each year, immunocompromised patients may contract one or more of the A/H1N1, A/H3N2, or B influenza viruses, while the specific strains change by so-called antigenic drift (minor changes in the existing strains) or shift (new strains). The 2009 influenza pandemic raised awareness of the importance of influenza viruses among both the general and immunocompromised populations, including leukemic and post-hematopoietic stem cell transplantation (HSCT) patients, in whom severe disease and mortality were reported (1). These patients are recognized to be at increased risk for complicated and even fatal influenza A and B.

The European Conference on Infections in Leukemia (ECIL) has a primary goal of developing recommendations for managing infections in hematology patients (2). At the fourth ECIL meeting, September 2011, participating experts prepared and discussed guidelines for prevention and management of influenza in patients with hematological malignancies and after HSCT, based on the published literature. This review summarizes their main recommendations.

Materials and methods

The methodology of ECIL conferences has been described (2). It includes the following categories: epidemiology, diagnosis, clinical manifestations, risk factors for severe and complicated influenza, and treatment and prevention, including vaccination and infection control measures.

These categories were addressed by the working group that reviewed the published English-language literature, containing the following key words: influenza and leukemia, bone marrow transplantation, stem cell transplantation. Based on the published data, they prepared proposals for preventing and managing influenza in leukemic and HSCT patients. The quality of evidence and strength of recommendations were graded according to the Infectious Diseases Society of America system (3) (Table 1).

Epidemiology

Community respiratory viruses, such as respiratory syncytial virus, influenza viruses, parainfluenza viruses, adenoviruses, and picornaviruses, are important causes of respiratory disease in the immunocompromised host. Leukemic and HSCT patients are usually infected with influenza virus in the community during the annual influenza seasons. In addition, outbreaks of nosocomial influenza were reported in hematology departments with leukemic patients (4) and in bone marrow transplant (BMT) departments (5). During the 2009 influenza pandemic, despite infection control measures, nosocomial transmission of influenza A/H1N1 in hematology departments and HSCT units was common (1, 6–8).

Clinical manifestations of influenza

Influenza usually starts as acute onset of fever, usually accompanied by chills, myalgia, and non-productive cough, although approximately 20% of HSCT patients have confirmed influenza without fever (1). Myalgia and respiratory symptoms can be completely absent and influenza may occur without any typical systemic signs and symptoms. A similar proportion of afebrile patients has been reported in solid organ transplant recipients (9). In time, symptoms of upper respiratory infection, including throat pain, nasal congestion, coryza, and cough, may become more prominent. Conjunctival congestion, abdominal pain, nausea, vomiting, and diarrhea may also be present, with myositis sometimes developing, resulting in difficulty walking. Infants may present with sepsis symptoms, and respiratory tract involvement, including laryngitis and pneumonia.

Pneumonia is the main complication of influenza, sometimes with acute and potentially fatal respiratory distress syndrome. Neurological complications include a variety of symptoms – among them, encephalopathy and encephalitis that may lead to neurological sequelae and even death. Myocarditis may also develop. An important neurologic complication associated with influenza infection itself (non-vaccine related) is the developing Guillain-Barré syndrome, with an estimated incidence of 40–70 cases per 1,000,000 cases of influenza. By way of comparison, risk of developing

Quality and strength of the recommendation

Quality of evidence	Strength of recommendation
I. Evidence from ≥ 1 properly randomized, controlled trial	A. Good evidence to support a recommendation for or against use
II. Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments	B. Moderate evidence to support a recommendation for or against use
III. Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C. Poor evidence to support a recommendation

Base on the Infectious Diseases Society of America guidelines (3).

Table 1

Guillain-Barré syndrome after influenza vaccination is 1–2 cases per 1,000,000 vaccinations (10).

In patients with acute leukemia, influenza A may cause hemophagocytic syndrome (11). This syndrome was associated with high mortality rate in the 2009 A/H1N1 influenza pandemic (12). Severe influenza-induced rhabdomyolysis was also reported after HSCT (13).

Clinical manifestations of the pandemic A/H1N1 2009 influenza in post-HSCT patients, as found in 286 patients in Europe, included cough (85%), fever (81%), coryza (49%), myalgia (29%), respiratory distress (25%), gastrointestinal symptoms (12%), and neurological signs (4%) (1).

Diagnostic techniques

Qualitative reverse transcriptase multiplex real-time polymerase chain reaction (RT-PCR) is considered the most sensitive and specific test and is, therefore, the current gold standard laboratory method of confirming diagnosis of influenza and other respiratory viruses, both in the general population (14) and in immunocompromised hosts. RT-PCR can double the yield of positive specimens relative to culture and more than quadruple them relative to fluorescent antibody staining (15).

Quantitative PCR detects high viral loads in bronchoalveolar lavage samples from HSCT recipients with viral pneumonia. In addition, viral RNA may be detectable in the serum of patients with influenza pneumonia and may correlate with the severity of disease (16). PCR may also be important in detecting asymptomatic or mildly symptomatic cases.

Rapid influenza diagnostic tests (RIDTs) have high specificity (>90%), but low-to-moderate sensitivity (10–80%) compared with viral culture or RT-PCR (14, 17). As a consequence, influenza can be diagnosed, but not ruled out through the use of RIDTs. Moreover, sensitivity varies across populations, higher in children than adults, and higher for influenza A than B. No important differences in the accuracy of the RIDTs were found between studies conducted during the influenza A (H1N1) 2009 pandemic and those conducted before it (17).

Morbidity and mortality due to influenza

Several reports have been published about severe morbidity of seasonal influenza in leukemic patients and HSCT recipients, especially from outbreaks during hospitalization and during the 2009 pandemic. The main reports are summarized in Table 2 (1, 4, 18–22).

In a study conducted during the 1991/1992 influenza season, signs and symptoms of acute upper or lower respiratory tract infection (LRTI) developed in 37/294 adult leukemia patients (13%). Among these, the influenza A/Beijing/H3N2 strain caused 4 infections (11%) (4).

During the 1993/1994 season, among 15/45 (33.3%) adult leukemic US patients with acute respiratory illness due to A/H3N2 influenza (12 [80%] of them with pneumonia), 4 (27%) patients died (18).

Children with leukemia usually survived the 2009 A/H1N1 influenza pandemic, including those who developed pneumonia and those who needed mechanical ventilation (23–26), although some fatalities occurred (27). In adults with hematologic diseases, one center reported 5/11 (45%) patients who developed pneumonia and died of 2009 A/H1N1 influenza, despite treatment with antivirals and/or corticosteroids and/or mechanical ventilation (19).

During the 1991/1992 influenza epidemic, influenza virus type A was isolated in 8/28 (29%) HSCT recipients with acute respiratory illness, 6 of them with pneumonia. The frequency of influenza was similar among autologous (5 of 18) and allogeneic (3 of 10) HSCT recipients. Mortality in patients with pneumonia was 17% (20).

In a prospective European Group for Blood and Marrow Transplantation study involving 37 European centers (1997–2000), the frequency of documented respiratory virus infections among HSCT patients transplanted during the study period was 3.5% among 819 allogeneic and 0.4% among 1154 autologous transplants. Overall mortality due to influenza was 23.0%, and direct influenza-associated mortality was 15.3% (21).

In a retrospective study covering 14 years, influenza was diagnosed in 1.3% of 4797 HSCT recipients. Pneumonia developed in 18 (29%) of them, mainly those who were untreated. The 30-day mortality rate was highest among patients who had progression to pneumonia (5/18 [28%] patients). Furthermore, pulmonary co-pathogens (such as *Aspergillus fumigatus*) were commonly detected (22).

Other studies of community respiratory viruses (28–32) and earlier reports focusing on influenza (33, 34) also indicate the important role of the influenza virus as a cause of morbidity and mortality in leukemic patients and HSCT recipients.

Some centers report relatively mild 2009 A/H1N1 influenza disease in HSCT recipients, mainly in children (35, 36), with others reporting severe pandemic A/H1N1 2009 influenza (8, 37–42). The largest study of the pandemic A/H1N1 2009 influenza included 64 European HSCT centers reporting 286 patients, 222

Influenza in leukemia and hematopoietic stem cell transplant (HSCT) patients – morbidity and mortality (main reports)

Authors, year (ref.)	Setting	Occurrence	Morbidity	Mortality
Elting et al., 1995 (4)	A prospective study of 294 adult leukemia patients undergoing remission-induction chemotherapy during the 1991/1992 influenza season	Influenza A/Beijing/H3N2 was found In 4/37 (11%) patients with acute respiratory illness		
Yousuf et al., 1997 (18)	A prospective study of hospitalized leukemic adults; during 9 weeks of the 1993/1994 influenza season	Influenza A/H3N2 was found in 15/45 (33.3%) patients with acute respiratory illness; 2 were nosocomial	12/15 (80%) had pneumonia	4/15 (27%) died
Wei et al., 2010 (19)	A retrospective report of 11 adults with hematological diseases hospitalized with 2009 A/H1N1 influenza		9/11 (82%) patients developed pneumonia	5/11 (45%) died
Whimbey et al., 1994 (20)	A prospective study of 68 adult HSCT recipients during the 1991/1992 influenza season	Influenza (A/Beijing/H3N2) was found in 8/28 (29%) patients with acute respiratory illness; 5 were nosocomial	6/8 (75%) patients developed pneumonia	1/8 (12.5%) died
Ljungman et al., 2001 (21)	A prospective EBMT study involving HSCT recipients in 37 European centers (1997–2000)	Influenza occurred in 3.5% of allogeneic HSCT and 0.4% of autologous HSCT patients		Direct influenza-associated mortality was 15.3%
Nichols et al., 2004 (22)	A retrospective study summarizing 14 years (1989–2002) in HSCT recipients	Influenza was diagnosed in 62/4797 (1.3%) of HSCT recipients	18/62 (29%) developed pneumonia	5/18 (28%) died
Ljungman et al., 2011 (1)	A study of the pandemic A/H1N1 2009 influenza; 64 European centers: 286 patients: 222 allogeneic and 64 autologous HSCT patients	125/286 (44%) patients were hospitalized	93/286 (33%) developed LRTI; 16% needed mechanical ventilation	18/286 (6%) died

LRTI, lower respiratory tract infection; EBMT, European Group for Blood and Marrow Transplantation.

Table 2

after allogeneic transplantation and 64 after autologous HSCT. Patients were aged 3.3–72.3 (median 38.3) years, and the interval between transplantation and influenza was 0–204.9 (median 19.4) months. In total, 267 patients were treated with oseltamivir and 15 with zanamivir; 125 patients (44%) were hospitalized; 93 (33%) developed LRTI; 33 (16%) patients needed mechanical ventilation; and 18 (6%) patients died of the pandemic influenza or its complications 2–96 days after diagnosis (1).

Infection with 2009 influenza A/H1N1 resulted in more severe respiratory disease in HSCT recipients compared with seasonal influenza. In a retrospective study comparing 18 cases of 2009 A/H1N1 influenza with 103 seasonal influenza A infections and 40 seasonal influenza B cases, more patients with 2009 A/H1N1 had LRTI, hypoxemia, and prolonged viral shedding compared with seasonal influenza A. No difference was seen in overall and influenza-associated mortality among influenza virus types (43).

Risk factors

Several risk factors for complicated influenza in leukemia and HSCT patients were reported. These risk factors are summarized in Table 3 (1, 8, 18, 22, 31, 43). Because the quality of the statistical analyses in the papers listed varies widely, so too does the strength of the evidence. Some of these papers, for example, do not include multivariate modeling, which reduces the quality of the data.

Lymphopenia was found to be a risk factor for LRTI and for fatal outcome in several studies. The cutoff number of absolute lymphocytes differed in the different studies: $<100/\mu L$ (22, 43), $\leq 200/\mu L$ (31), or $<300/\mu L$ (1). In the European Group for Blood and Marrow Transplantation survey of common respiratory viruses after HSCT, lymphopenia increased the risk for LRTI of all documented respiratory virus infections (21). Viral LRTI in the first 100 days after HSCT was less common in those receiving non-myeloablative conditioning regimens compared with myeloablative conditioning, despite a similar overall rate of acquisition of respiratory viruses (44).

It has been suggested that high-dose corticosteroid treatment (≥ 1 mg/kg) given for graft-versus-host disease (GVHD) at the time of influenza A diagnosis may decrease the need for mechanical ventilation (43), but this is controversial; and it was not found in multivariable analyses of an earlier study of the same HSCT center (45). In addition, chronic steroid use (≥ 20 mg/day of prednisone equivalent) at the time of presentation was significantly associated with LRTI and mortality in univariate analysis of another study performed by two U.S. HSCT centers (8). The experience of intensive care departments with steroid use in the 2009 A/H1N1 influenza pandemic also argues against its use. In a prospective, observational, multicenter study of 220 patients carried out by the European Society of Intensive Care Medicine, early use of corticosteroids in patients affected by the pandemic 2009 A/H1N1 influenza infection did not result in better outcomes and was associated with increased risk of superinfections (46). In addition, in a retrospective study of 245 adult patients with confirmed 2009 A/H1N1 influenza admitted to the intensive care units of 28 hospitals in South Korea, adjuvant corticosteroids were significantly associated with higher mortality in these critically ill patients (47).

Additional risk factors for complicated influenza were lack of early antiviral therapy (43) for LRTI and fatal outcome; older age for LRTI (1); and influenza soon after chemotherapy or earlier after HSCT for fatal outcome. In allogeneic HSCT, a donor other than a sibling was an additional risk factor for influenza LRTI. Neutropenia and isolation of oseltamivir-resistant strain of 2009 A/H1N1 were also risk factors for mortality (1).

Viral shedding and emerging of resistance

Viral shedding is prolonged in leukemia and HSCT recipients. Shedding persisted for a median 12 days (range 8–13 days) in one study and the absolute lymphocyte count at diagnosis correlated inversely with the duration of shedding ($P < 0.001$) (48). It has also been found that viral secretion was longer in patients receiving >1 mg/kg steroids (22, 45).

Most influenza isolates are currently resistant to amantadine. Persistent influenza virus replication during antiviral therapy in leukemic and HSCT patients can promote the emergence of resistance to oseltamivir, mainly with H275Y mutation. This emergence was described both in A/H3N2 (49) and during the 2009 A/H1N1 influenza (38, 50). In the large European study of 286 HSCT recipients with 2009 A/H1N1, 7 strains of 75 tested (9.3% of tested strains; 2.4% of the entire population) were shown to be oseltamivir resistant (1).

Antiviral treatment

Neuraminidase inhibitors (oral oseltamivir or inhalation of zanamivir) are currently the most effective prophylactic and therapeutic agents for influenza. In one study

Risk factors for complicated influenza in leukemia and hematopoietic stem cell transplant (HSCT) patients

Authors, year (ref.)	Influenza	Patient population	Risk factor	Outcome
Yousuf et al., 1997 (18)	Seasonal	Leukemia	Influenza soon after chemotherapy	Fatal outcome
Nichols et al., 2004 (22)	Seasonal	HSCT	Infection earlier after transplantation Lymphopenia <100	Fatal outcome
Chemaly et al., 2006 (31)	Seasonal	HSCT recipients and patients with hematologic malignancies with pneumonia	Lymphopenia $\leq$200/μL	Fatal outcome Pneumonia and fatal outcome
Choi et al., 2011 (43)	Seasonal	HSCT recipients	Lymphopenia <100/μL Lack of early antiviral therapy	Pneumonia, hypoxemia and fatal outcome
Espinosa-Aguilar et al., 2011 (8)	2009 A/H1N1	HSCT recipients	Chronic steroid use ($\geq$20 mg/day of prednisone equivalent)	LRTI and fatal outcome
Ljungman et al., 2011 (1)	2009 A/H1N1	HSCT recipients	Older age Lymphopenia <300/μL Infection earlier after transplantation	LRTI
		Allogeneic HSCT recipients	Donor other than sibling	LRTI
		HSCT recipients	Neutropenia Increased age Isolation of oseltamivir-resistant strain of 2009 A/H1N1	Fatal outcome

LRTI, lower respiratory tract infection.

Table 3

of patients with leukemia, neuraminidase inhibitors were given to 25 patients, all of whom recovered. In contrast, 3 of 8 patients, who were untreated, died ($P = 0.001$) (51). There are other reports on effective early treatment with neuraminidase inhibitors in seasonal influenza, including in children during maintenance therapy for leukemia (52). A similar experience with leukemic children was reported with pandemic A/H1N1 2009 influenza (25).

The benefit of antiviral treatment has also been documented in HSCT recipients. In a retrospective study, 6 untreated patients (18%) developed pneumonia, whereas only 1 (13%) of 8 patients treated with rimantadine and 0 of 9 treated with oseltamivir developed pneumonia. Comparing seasonal strains and A/H1N1 influenza of 2009, both early and delayed administration of antiviral therapy initiated during the upper respiratory infection phase decreased rates of development of pneumonia ($P < 0.01$) and hypoxemia ($P = 0.03$), although earlier intervention appeared to be more effective (43, 45). Because of conditions such as GVHD of the gut or the lungs, absorption of the drugs may be lower.

Inhalation of zanamivir is a possible therapy for oseltamivir-resistant influenza with the H275Y mutation. For very sick patients during the 2009 A/H1N1 influenza pandemic, who could not absorb oseltamivir administered orally or via nasogastric tube and were unable to inhale zanamivir, intravenous zanamavir or intravenous peramivir were experimental options (53–57).

The recommended duration of therapy with neuraminidase inhibitors in leukemic and HSCT patients may be 10 days, as reoccurrence may develop with the 5-day course recommended for immune-competent hosts (58, 59). Longer therapy is necessary when symptoms do not resolve and viruses are not cleared from respiratory secretions (58).

Prevention

Vaccination

Patients with hematologic malignancies who receive chemotherapy at the time of vaccination are unlikely to attain optimal seroconversion to protective antibody

levels with influenza vaccine (60, 61). In children, during maintenance chemotherapy for lymphoblastic leukemia, most studies showed that antibody levels after vaccination are lower compared with controls or those off therapy. Nonetheless, significant numbers of children develop protective antibody levels. The killed vaccine was found to be safe, although local adverse effects occur frequently (62–68). The Cochrane database of systematic reviews recently summarized that inactivated influenza vaccine may reduce respiratory infections and hospitalization in children with leukemia or lymphoma (69); the quality of evidence is low, however.

One study, for example, showed that the geometric mean titers of the 3 vaccine strains in leukemic children were significantly lower than in controls. Nevertheless, 60% of the leukemic children seroconverted – at least a 4-fold rise in the antibody titers (66). Another study of seasonal influenza vaccine included 32 children with leukemia, aged 1–18 years, with 30 siblings as controls. The protective antibody levels in the leukemic children were 43.4% against A/H1N1, 66.3% against A/H3N2, and 23% against B influenza, versus 88%, 80%, and 76%, respectively, in the control group; all differences were statistically significant (68).

In HSCT recipients who received trivalent influenza subunit inactivated seasonal vaccine 2–82 months (median 14.5 months) after HSCT, regression analysis revealed that longer intervals between the BMT and immunization (protective antibody level $\geq$1:40) positively correlated with seroconversion. In the presence of GVHD, seroconversion to A/H1N1 was reduced, but not to A/H3N2 or B strains. Influenza vaccination within the first 6 months after BMT was ineffective. The specific humoral response was only marginally enhanced by a second dose of vaccine (70). Similar serological response rates in patients vaccinated at 4–12 months, as in those vaccinated >12 months after HSCT, have been described (71). These investigators also reported that a single dose of granulocyte-macrophage colony-stimulating factor improved the immune response to influenza vaccination in some groups of HSCT recipients (allogeneic or those with breast cancer). Another study showed a significant reduction in the rates of virologically confirmed influenza in HSCT recipients who were vaccinated 6 months or more after HSCT (2/19), compared with 12/24 unvaccinated patients – a protection rate of 80% (72).

Seasonal vaccination against influenza can boost the cellular immune response in HSCT patients as early as 3 months after HSCT, but the protective effect is lower compared with healthy controls – especially in those vaccinated early after HSCT (73).

During the A/H1N1 2009 influenza pandemic, the vaccine that was developed contained only the pandemic A/H1N1 strain. This vaccine was safe and well tolerated by both leukemia patients and HSCT recipients. Several studied have evaluated the responses to different 2009 H1N1 vaccines. In a comparison of adults with hematological malignancies with healthy controls, protective antibody titers of 1:32 or more were seen in 100% of controls, compared with 39% of patients with B-cell malignancies and 46% of allogeneic HSCT recipients. Following a second dose, seroprotection rates increased to 68% and 73% in patients with B-cell malignancies and those after allogeneic HSCT, respectively (74). T-cell responses to H1N1 vaccine were not, however, significantly different between patients and controls (74).

In children receiving 2 doses of an AS03(B)-adjuvanted vaccine, seroconversion rates of 33.3% (9 of 27) were found in those with acute lymphoblastic leukemia (75). In a study of 38 HSCT recipients who had either 2009 A/H1N1 infection or vaccination, 53% responded serologically. All vaccine recipients previously treated with rituximab were non-responders (76), as shown also in lymphoma patients (77). In a study of 82 allogeneic HSCT recipients vaccinated 2.5–94 (median 19) months after transplant, seroprotective antibody titers (hemagglutination inhibition titer $\geq$1:40) were detected in 51%. Patients were more likely to develop seroprotective titer the longer the interval since HSCT. The presence of chronic GVHD and type of conditioning regimen did not affect the rate of detection of seroprotective titers after vaccination, whereas rituximab administration during the year before vaccination was associated with a lack of seroprotective titer (78).

A study of 55 allogeneic and 23 autologous HSCT patients, aged 11–72 (median 50) years and vaccinated 1–290 (median 27) months after HSCT showed that, 3–4 weeks after the first vaccination, 44.2% of patients had protective antibody titers, and 48.8% were protected after 2 doses of vaccine. The protective levels were significantly associated with higher lymphocyte counts (measured as a continuous variable) and higher baseline titers; in allogeneic HSCT patients, an association was also seen with a sibling as donor (79).

Another study compared the response to 2 doses of the AS03-adjuvanted influenza H1N1/A/09 vaccine in 65 allogeneic HSCT recipients, with a single dose given to 138 healthy controls. After 2 doses, HSCT patients achieved similar seroprotection rates (84% vs. 87%, $P = 0.65$) and antibody titers (305 vs. 340, $P = 0.88$) as controls after 1 dose. Multivariate analysis identified transplant-to-vaccination interval and active GVHD as the most powerful negative predictors of antibody

responses ($P = 0.04$ and $P = 0.002$, respectively) (80). In an additional study of 17 HSCT patients (14 allogeneic and 3 autologous HSCT), vaccinated with AS03-adjuvanted pandemic H1N1 influenza vaccine (11 received 2 doses), the rate of seroconversion was 41.2% after dose 1 and 81.8% after dose 2 (81).

Other preventive measures

Prophylaxis with a neuraminidase inhibitor can prevent influenza infection. Oseltamivir prophylaxis (75 mg/day), given for a median 17 (range, 10–81) days, appeared to be safe and well tolerated in managing a seasonal influenza outbreak in an HSCT outpatient residence, with no new cases of influenza A occurring in the facility (82). In a randomized placebo-controlled study in HSCT and solid organ transplant recipients, oseltamivir prophylaxis for 12 weeks during the period of influenza circulation was generally well tolerated and reduced culture- or PCR-confirmed influenza incidence (83).

Seasonal influenza vaccination of household contacts (excepting infants <6 month old) and health-care workers with all patients at risk for severe influenza is recommended by health authorities worldwide. General precautions to avoid transmission of respiratory viruses (including good personal hygiene, frequent hand washing, covering mouth and nose when coughing or sneezing, and safe disposal of oral and nasal secretions) are also recommended. Leukemia patients and patients after HSCT should avoid contact with individuals showing symptoms or signs of influenza-like illness (ILI), acute respiratory infection, and other community respiratory viruses, in the hospital and in the community.

It has been shown that education of patient and family pre-HSCT increases awareness of respiratory virus prevention strategies and household influenza vaccination, thereby reducing influenza risk after HSCT. Furthermore, household vaccination at HSCT admission was 71% for attendees and 30% for non-participants ($P < 0.0001$) (84).

ECIL 4 guidelines

Definitions

For the purpose of our recommendations, we used the European Centre for Disease Prevention and Control influenza case definitions, including clinical, laboratory, and epidemiological criteria (85), with modification of the laboratory methods.

Clinical criteria

Any person with at least one of the following clinical forms: ILI and acute respiratory infection (ARI).

- *ILI*: Sudden onset of symptoms, AND at least 1 of the following 4 systemic symptoms: fever or feverishness, malaise, headache, myalgia; AND at least 1 of the following 3 respiratory symptoms: cough, sore throat, shortness of breath.
- *ARI*: Sudden onset of symptoms, AND at least 1 of the following 4 respiratory symptoms: cough, sore throat, shortness of breath, coryza; AND, a clinician's judgment that the illness is caused by an infection.

Diagnostic techniques

Pooled bilateral nasopharyngeal and throat swabs rather than nasal wash are the preferred technique to obtain respiratory specimens (86, 87), although nasal wash also works well. Qualitative PCR of respiratory specimens is the recommended laboratory method of confirming a diagnosis of influenza. Other techniques have lower sensitivity and should be used only when PCR is unavailable. Known mutations causing resistance, such as H275Y mutation, can be detected using RT-PCR.

Epidemiological criteria: an epidemiological link by human-to-human transmission

Confirmed case: Anyone meeting the clinical (ILI or ARI) and the laboratory criteria.
Probable case: Anyone meeting the clinical criteria (ILI or ARI) and with an epidemiological link.

General precautions to avoid transmissions of respiratory viruses

Good personal hygiene should be observed, including frequent hand washing, covering mouth and nose when coughing and sneezing, and safe disposal of oral and nasal secretions (A-II; see Table 1). Leukemia patients and patients after HSCT should avoid contact with individuals showing symptoms or signs of ILI, ARI, and other community respiratory viruses, in the hospital and in the community (A-II).

Influenza vaccination

Annual influenza vaccination with the trivalent inactivated vaccine is generally recommended for

Influenza vaccination – ECIL-4 recommendations

Allogeneic/autologous hematopoietic stem cell transplant (HSCT) recipients

- Yearly vaccination with seasonal trivalent inactivated influenza vaccine is recommended in allogeneic and autologous HSCT recipients. (A-II)*
- The vaccine is preferably given prior to the influenza season, usually at least 3 months after HSCT. (B-III)
- A second dose of vaccine after 3–4 weeks is advised, although it may only have marginal benefit. (B-II)
- No data exist about live attenuated influenza vaccine (LAIV) safety and efficacy in HSCT patients, and it should not be used. (A-III)

Acute lymphoblastic leukemia/acute myeloid leukemia non-transplanted patients

- Vaccination with seasonal trivalent inactivated influenza vaccine is recommended after intensive chemotherapy has been discontinued, as well as for ALL children on maintenance therapy, when the peripheral granulocyte and lymphocyte counts are >500/μL. (B-II)
- As there are no data for LAIV safety and efficacy in HSCT patients, it should not be used. (A-III)

Household contacts and hospital staff

- Family members** and those in close contact with HSCT recipients should be immunized in the first year after HSCT and continue to be vaccinated annually as long as the recipient is at risk. (A-II)
- Immunization of the household contacts** of leukemic patients with killed influenza vaccine is advised during the chemotherapy period and shortly after. (C-III)
- Annual seasonal influenza vaccination is strongly recommended for all health-care workers of HSCT recipients and non-transplant leukemic patients. (A-II)
- HSCT and leukemia patients' household contacts and care providers should not be immunized with LAIV, because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the patients. (B-III)
- If vaccinated, household contacts, care providers, and visitors should refrain from contact with HSCT and leukemia patients for 7 days after immunization with LAIV. (B-III)

*Grading system, see Table 1.
**Influenza vaccine should not be given to infants <6 months old. In some countries, vaccine is not recommended for children of any age.

Table 4

immunocompromised patients, hospital staff, and household contacts. Live attenuated influenza vaccine should not be used. The ECIL recommendations are summarized in Table 4.

Post-exposure antiviral prophylaxis and antiviral treatment of influenza

ECIL recommendations for antiviral prophylaxis and therapy of influenza are shown in Table 5.

Discussion

Influenza can cause significant morbidity and mortality in patients with leukemia and in those after HSCT. Efforts should therefore be made to prevent exposure of these patients to individuals infected with influenza. Patients are at higher risk when they are lymphopenic, which is usually – but not exclusively – during and shortly after chemotherapy. It is to be hoped that centers will follow our recommendation about educating patients, their household contacts, family members, and health-care workers to increase vaccination rates, and otherwise do all they can to avoid transmission of influenza and other community respiratory viruses. Although vaccination is the main protective measure, vaccination early after intensive chemotherapy or HSCT may be ineffective, and its efficacy is only limited at a later stage. It is not known whether the live attenuated influenza vaccine is permanently contraindicated after HSCT, but as there is a good alternative, we recommend against its use even after full immune reconstitution. Future studies will show whether new vaccines, such as the intradermal influenza vaccine or adjuvanted vaccines, promote a better immune response. In 3 recent studies (74, 80, 88), adjuvanted vaccine had no impact on GVHD, a theoretical concern that has not been conclusively addressed, but is not supported by existing data. Meanwhile, post-exposure antiviral prophylaxis, currently with oseltamivir, is recommended. Because of the risk of increasing resistance to antiviral agents, we do not recommend administration of oseltamivir throughout the influenza season.

When a leukemic patient or HSCT recipient develops symptoms or signs of ILI or ARI, in the hospital or in the community, efforts should be made to obtain a specific diagnosis. During influenza seasons or pandemics, if lab testing is not feasible or available in

Antiviral prophylaxis and therapy of influenza – ECIL-4 recommendations

- Post-exposure antiviral prophylaxis, currently with oseltamivir, for at least 10 days is advised for hematopoietic stem cell transplant (HSCT) recipients who are <12 months after transplant, or later for those who are substantially immunocompromised, regardless of vaccination history, after exposure to a confirmed or probable case of influenza. (C-III)*
- Post-exposure antiviral prophylaxis for at least 10 days is advised for all acute lymphoblastic leukemia/acute myeloid leukemia (ALL/AML) patients during chemotherapy, regardless of immunization status of the patient, after exposure to a confirmed or probable case of influenza. (C-III)
- Efforts should be made to confirm all suspected and probable cases of influenza. (A-III)
- All allogeneic/autologous HSCT recipients and ALL/AML patients with confirmed or probable influenza during chemotherapy and the 6 months following it should be treated. (A-II)
- Preferred first-line treatment is oseltamivir, at an adult dose of 75 mg twice daily (BID) for a mild case and 150 mg BID for severe disease, administered for at least 10 days. (B-II)
- In patients with continuing symptoms, it is advised to repeat polymerase chain reaction tests on respiratory specimens every 5–7 days and to continue treatment until they become negative. (C-III)
- In severe or prolonged influenza disease, influenza resistance to antiviral drugs should be suspected and tests should be done every 5–7 days until improvement. (B-III)
- The current alternative treatment is inhaled zanamivir. (B-II)
- In severe influenza, when the gut absorption of oseltamivir is impaired and inhalation of zanamivir is not possible, intravenous peramivir or zanamivir may be alternative options. (C-III)

*Grading system, see Table 1.

Table 5

a timely manner, empiric therapy for probable and even possible influenza should be considered, especially if cases are detected within the care facility. Increased awareness and the availability of oseltamivir and zanamivir during the 2009 A/H1N1 influenza pandemic may explain the difference in mortality rates reported in the 2 large multicenter European HSCT studies: 6.3% in the 2009 A/H1N1 influenza pandemic (1), with an estimated rate of 15.3% for the previous seasonal influenza A (21). This difference is despite the fact that the pandemic influenza caused more severe LRTIs and pneumonia (43). Antiviral therapy is effective, especially when it is given early. Even when started late (after 48 h), however, therapy confers benefit (43, 45).

The controversy about risk versus potential beneficial effect of steroids needs further evaluation, with a randomized trial required to determine whether steroids help or hinder.

In adults with seasonal influenza A, mainly H3N2, virus infection, the oseltamivir-zanamivir combination appeared less effective than oseltamivir monotherapy, and not significantly more effective than zanamivir monotherapy. This combination should not, therefore, be used (89). The concept that a triple-combination regimen of amantadine, ribavirin, and oseltamivir would markedly reduce the risk of antiviral resistance emergence in seasonal and pandemic influenza viruses, especially in seriously ill or immunocompromised hosts, is attractive and advocated by several experts (90, 91). This regimen is supported by *in vitro* data (92) and in mouse models, inclusive of treatment delayed until 72 h after infection (93). However, clinical data are currently lacking. Furthermore, no benefit of triple-combination antiviral drug therapy with amantadine, oseltamivir, and ribavirin was found, over monotherapy with oseltamivir, for pandemic H1N1 influenza virus infection in critically ill patients on mechanical ventilation (94). Therefore, a recommendation for triple antiviral agents–amantadine, oseltamivir, and ribavirin –for severe influenza in leukemia patients and HSCT recipients, or in influenza with highly pathogenic influenza A strain, such as H5N1, awaits additional clinical data.

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